AF-

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,297	03/05/2002	Bruno Tocque	50146/002002	2833

21559 7590 11/18/2005

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
SISSON, BRADLEY L	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 11/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,297	TOCQUE ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2005 and 28 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27,29-33,44 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27,29-33,44 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 21 July 2005 has been entered.

Specification

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

3. The specification is objected to as documents have been improperly incorporated by reference. It is noted with particularity that the instant disclosure makes reference to various foreign patent document, both published and unpublished, as well as non-patent publications, which are in turn being relied upon for disclosing how the claimed invention is to be made and used. In support of this position, attention is directed to page 17, lines 15-17, reproduced infra.

> To take into account these phenomena and this complexity, and to thereby isolate signatures that are specific to a pathological state and present in blood cells, the process of the invention advantageously makes use of splicing events characteristic of situations of deregulation, as genetic markers.
>
> To do so, the present invention uses, for example, differential qualitative nucleic acid banks produced according to "DATAS" methodology described in the unpublished international patent application PCT/FR 99/00547. In

4. See also page 18, lines 17-24; page 19, lines 17-19; page 20, lines 11-14; and page 28, lines 12-14. It is noted with particularity that page 17, lines 15-17, teaches that one is to employ the method disclosed in an unpublished international patent application; and that hybridization is to be "advantageously carried out...according to the method described by Miller and Riblet (NAR 23 (1995) 2339)" (page 18, ll. 20-24). Also, page 18, second paragraph, states in part:

> According to a specific embodiment of the invention, the hybridization is carried out in a phenol emulsion, for example according to the PERT method ("Phenol Emulsion DNA Reassociation Technique) described by Kohne D.E. et al. (Biochemistry, Vol. 16, No. 24, pp 5329-5341, 1977). The hybridization is avantageously carried out in a phenol emulsion maintained by thermocycling (temperature increase from approximately 37°C to approximately 60/65°C) and not by agitation, according to the method described by Miller and Riblet (NAR 23 (1995) 2339).

Attention is also directed to page 19, which states in part:

> It is understood that other specific variants and conditions for the isolation of nucleic acids, hybridization and obtaining of qualitative clones, are indicated in the not-yet-published application No. PCT/FR99/00547.

Such language fails to specify what specific information applicant seeks to incorporate by reference and just where that specific information is to be found in each of the cited documents. As set forth in *Advanced Display Systems Inc. v. Kent State University* (Fed. Cir. 2000) 54 USPQ2d at 1679:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes it clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USQP 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). **To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.** *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-02, 170 USPQ 213, 216-17 (CPA 1971) (reasoning that a rejection or anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order to have that material considered a part of a later application); *cf. Lund*, 376 F.2d at 989, 13 USPQ at 631 (holding that **a one sentence reference to an abandoned application is not sufficient to incorporate from the abandoned application into a new application**). (Emphasis added.)

5. Attention is also directed to MPEP 608.01(p)I, which, in pertinent part, is reproduced below:

> Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. In re de Seversky, 474 F.2d 671, 177 USPQ 144 (CCPA 1973). In addition to other requirements for an application, the referencing application should include an identification of the referenced patent, application, or publication. Particular attention should be directed to specific portions of the referenced document where the subject matter being incorporated may be found. (Emphasis added)

6. Accordingly, the cited documents are not considered to have been properly incorporated by reference and as such, have not been considered with any effect towards their fulfilling, either

in part or in whole, the enablement, written description, or best mode requirements of 35 USC 112, first paragraph.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

8. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

9. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 27, 29-33, 44 and 46 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,372,432 B1 (Tocque et al.). Although the conflicting claims are not identical, they are not

patentably distinct from each other because both sets of claims are drawn to methods of detection of pathological conditions.

Response to argument

11. Acknowledgement is made of where at pages 13-14 of the response of 21 July 2005, hereinafter the response, applicant's representative agrees to provide a terminal disclaimer "once otherwise allowable subject matter has been determined."

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 27, 29-33, 44, and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Attention is directed to the decision in *University of Rochester v. G.D. Searle & Co.* 68 USPQ2D 1424 (Fed. Cir. 2004) at 1428:

> To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Vas-Cath, 935 F.3d at 1563; see also Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"); In re Gosteli, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) ("the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written-description requirement "by describing the

invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572.

14. For convenience, claim 27, the sole independent claim, is reproduced below.

27. (Currently Amended) A method for the detection *in vitro* of the presence of a given, predefined pathological condition in a human ~~mammalian~~ subject, said method comprising:

(i) providing a sample of blood cells from the subject, wherein said blood cells comprise lymphocytes, macrophages, monocytes or dendritic cells,

(ii) preparing nucleic acid molecules from the sample, and

(iii) obtaining a hybridization profile by hybridizing all or part of the nucleic acid molecules so prepared with at least one nucleic acid library ~~in order to obtain a hybridization profile, the nucleic acid library~~ comprising a plurality of nucleic acid molecules specific for differentially spliced ribonucleic acid molecules (RNAs) exprcssed ~~gene products present~~ in ~~mammalian~~ blood cells from human subjects having the given, predefined pathological condition, wherein expression of the differentially spliced RNAs is characteristic of the given, predefined pathological condition ~~the same species as said subject~~, and wherein said blood cells from human subjects having the given, predefined pathological condition comprise lymphocytes, macrophages, monocytes, or dendritic cells ~~exposed to or experiencing a pathological condition~~, the hybridization profile indicating the presence of said given, predefined pathological condition in said subject.

15. A review of the disclosure finds that at page 7, last paragraph, bridging to page 8, the "pathologies" contemplated by applicant which could be detected by the claimed invention

> As noted above, the process of the invention can be implemented for the detection of different types of pathologies, notably pathologies associated with deregulation of cell signalling pathways. These may be pathologies related to ageing, such as neurodegenerative disorders for example, or any other pathology involving particularly an abnormal level of cell proliferation, such as cancer, stenosis, etc.
>
> In another specific embodiment, the invention concerns a process such as defined above for the detection in vitro of the presence, the stage of progression and/or the site of a cancerous disease. These may be different types of cancer such as, for example, solid tumors of the liver, lungs, head and neck, melanoma, liver, bladder, breast, etc. (Emphasis added.)

16. A review of the specification fails to find where applicant had contemplated, much less fully described, pathologies other than cancer, stenosis and neurodegenerative disorders as being applicable to a general method of detecting pathologies in organisms, much less to detecting such pathologies in humans and then using only lymphocytes, macrophages, monocytes or dendritic cells, to which clam 27is now limited. Indeed, the specification has not identified any specific form of cancer that can be identified from these cells, much less teach what an informative hybridization profile would look like.

17. While an applicant is not required to provide examples of their invention, it is noted that the only part directed to diagnosis of pathologies in humans is that found at pages 28-30, and then the disclosure is found to contain numerous instances of employing forward-looking statements a to what is "possible" and/or "very probable." Neither pages 28-30 nor any other part of the disclosure has been found to set forth a full, clear, and concise description of the invention such that one would be able to identify any human cancer, much less cancers such as solid tumors of the liver, lungs, head and neck, melanoma, liver, bladder, breast, etc., or for that matter, any other human pathology.

18. Absent the requisite description, and having found in its absence numerous instances of forward-looking statements, the specification does not reasonably suggest that applicant was in possession of the invention at the time of filing.

19. Therefore, and in the absence of convincing evidence to the contrary, claims 27, 29-33, 44, and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

20. Claims 27, 29-33, 44, and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737,

> 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

21. The claimed method is directed to, and encompasses the detection *in vitro* of any given predefined pathological condition in a human. For purposes of examination, the "predefined pathological condition" has been interpreted as encompassing any disorder that originates in any tissue of any human, including, but not limited to alcoholism, diabetes, autism, cancer, autoimmune disorders, gingivitis, heart disease, etc.

22. A review of the specification fails to find where any hybridization profile has been determined for any known human pathological condition.

While one is note required to teach each and every possible embodiment encompassed by the claims, the specification has not been found to teach a reproducible method whereby any specific human pathological condition could be identified. In short, applicant has not provided the essential starting materials and reaction conditions needed to practice even a part of the claims' scope. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
>
> *****

> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. <u>However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art.</u> It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research. (Emphasis added)

23. Furthermore, and as set forth above, the specification does not reasonably suggest that applicant was in possession of the claimed invention at the time of filing. Given that one cannot enable that which they do not yet possess, the instant claims are not enabled by the original disclosure.

24. Therefore, and in the absence of convincing evidence to the contrary, claims 27, 29-33, 44, and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

<u>Response to argument</u>

25. At page 7, bridging to page 8 of the response applicant's representative assert that the teachings of Miller and Riblet are not needed to enable the claimed invention and that the post-

filing publication of PCT/FR99/00547 can now be relied upon by those of skill in the art as "background."

26. The above arguments have been fully considered and have not been found to be persuasive towards the withdrawal of the rejections. As set forth under 35 USC 112, first paragraph, applicant must fulfill three requirements: 1) written description, 2) enablement, and 3) best mode contemplated by applicant at the time of filing. Page 18, second paragraph, of the specification teaches that the method of hybridization "advantageously carried out" in accordance with that disclosed by Miller and Riblet. Such emphasis on the part of applicant is construed as teaching the best mode contemplated. As noted above, however, this document has not been incorporated by reference and its disclosure is not now, nor can it be brought into the instant disclosure so to overcome this deficiency.

27. Similarly, page 17 of the disclosure teaches that "differential qualitative nucleic acid banks [are] produced according to 'DATA' methodology described in the unpublished international patent application PCT/FR99/00547." Again, the directing of attention to this preferred method is construed as disclosing the best mode contemplated. While applicant's representative has asserted that other methods are available to the public, the specification, as originally filed, directs one to these methods, which as shown above, are not fully described or enabled.

28. While agreement seems to be reached in that one does not necessarily need to know the nucleotide sequence of the relevant target and probes, one must know the relevant hybridization profiles. Such disclosure is not provided in the original disclosure. Furthermore, the aspect of

narrowing the claims to where the profile and condition are "predetermined" does not overcome the issue of the specification not providing such essential starting materials.

29. For the above reasons, and in the absence of convincing evidence to the contrary, claims 27, 29-33, 44, and 46 are rejected under 35 U.S.C. 112, first paragraph.

Conclusion

30. Objections and/or rejections which appeared in the prior Office action and which have not been repeated hereinabove have been withdrawn.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

32. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (571) 272-0745. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

33. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1634

15 November 2005
BLS